Lung and Thymic Carcinoids

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KEYWORDS

• Carcinoid • Lung carcinoid • Lung neuroendocrine • Thymic neuroendocrine
• Thymic carcinoid

KEY POINTS

- Lung carcinoid tumors are indolent cancers with a good prognosis; after appropriate staging, tumors localized to the lung are treated with surgical resection. The role of adjuvant therapy after surgical resection has not been clearly defined.
- Definitive radiation or chemoradiation may be considered for patients with unresectable atypical carcinoid, although evidence to support this approach is limited.
- Somatostatin analogue therapy should be considered for patients with advanced thoracic carcinoids that expresses somatostatin receptors.
- Everolimus is the only approved systemic therapy for patients with advanced pulmonary carcinoid.
- Chemotherapy agents, including temozolomide with or without capecitabine, may be options for patients whose tumors progress despite these approaches. Lutetium-177–dotatate has demonstrated efficacy in gastrointestinal neuroendocrine tumors and, where available, may be considered for patients with advanced somatostatin receptor–positive lung carcinoid.

The goal of early stage disease management is definitive surgical resection. Definitive radiation or chemoradiation may be considered for locally advanced pulmonary carcinoids or thymic neuroendocrine tumors, although evidence to support this approach is limited.

Systemic therapy for advanced or metastatic pulmonary carcinoids generally follows a similar paradigm to low-grade carcinoid tumors of the gastrointestinal (GI) tract. Somatostatin analogue therapy is an option for receptor-positive tumors. Similarly, peptide receptor radionuclide therapy (PRRT) with lutetium-177 (^{177}Lu)–octreotate may be considered. Everolimus has been approved for treatment of patients with

Disclosures: C.L. Hann: consulting/advisory role: AbbVie, BMS, Genentech; research funding (to institution): GSK, Merrimack, AbbVie, BMS. P.M. Forde: consulting/advisory role: BMS, AstraZeneca, Novartis, Merck, Abbvie; research funding (to institution): BMS, AstraZeneca, Novartis, Kyowa.

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Endocrinol Metab Clin N Am 47 (2018) 699–709
https://doi.org/10.1016/j.ecl.2018.04.011 **endo.theclinics.com**

advanced pulmonary carcinoid, and systemic chemotherapy has shown responses in small series.

LUNG CARCINOIDS

Introduction

Neuroendocrine tumors (NETs) account for approximately 20% of all cancers arising in the lung and include a spectrum of pathologies from well-differentiated tumors (typical and atypical carcinoids) to poorly differentiated carcinomas (small cell lung cancer [SCLC] and large cell neuroendocrine carcinoma [LCNEC]). The classification of NETs is based on microscopic, macroscopic, and immunohistochemical staining. Despite similarities in morphologic and biochemical characteristics, the behavior and natural history of carcinoid tumors are dramatically different from that of SCLC and LCNEC. This review focuses on the low-grade NETs of the lung and thymus, also known as carcinoid tumors.

Incidence and Epidemiology

The lung is the second most common site of carcinoid tumors, accounting for 25% of overall cases. Pulmonary carcinoids, however, are considered rare lung neoplasms, estimated at 1% to 2% of all primary lung cancers.[1] Typical carcinoids are more common than atypical carcinoids (85% vs 15% cases) and have a lower likelihood of metastatic spread or relapse after surgery; therefore, they carry an overall better prognosis.[2–4] The average age of diagnosis for lung carcinoids is 60 years; patients with typical carcinoids usually present a decade earlier than those with atypical carcinoids.[5–7] Pulmonary carcinoids occur more commonly in women than in men and are not clearly attributed to tobacco exposure.[2,5,8] Pulmonary carcinoids can rarely occur in association with multiple endocrine neoplasia type 1 (MEN-1) syndrome.

Presentation

Most carcinoid tumors arise from the proximal airways, and presenting symptoms may be due to local obstruction (cough, dyspnea, atelectasis); hemoptysis presents in 10% to 20%.[2,9] NETs can produce a variety of biologically active peptides and hormones, some of which lead to clinically relevant syndromes. The carcinoid syndrome, due to the production of serotonin and bioactive amines, is less common in patients with lung carcinoids (<10% of cases) than in patients with midgut (small bowel, appendix, and ascending colon) NETs.[10] A detailed discussion and recommendations on the management of the carcinoid syndrome is covered in Paul Benjamin Loughrey and colleagues' article, "New Treatments for the Carcinoid Syndrome," in this issue. Lung NETs are the most common cause of ectopic adrenocorticotropic hormone (ACTH) production; thus, Cushing syndrome may be a presenting symptom of this disease, though the overall incidence in lung carcinoids is rare (1%–2% of cases).[11] Lung carcinoids are also the most common site of extrapituitary secretion of growth hormone–releasing hormone; thus, patients with lung NETs may rarely present with acromegaly.[12]

Diagnosis and Staging

Core biopsies are preferred for histopathologic diagnosis, as a definitive diagnosis may be difficult to ascertain in cytology samples, particularly in differentiating typical versus atypical carcinoid tumors. Pulmonary carcinoids are categorized as typical or atypical corresponding to well differentiated, low grade (G1) and well differentiated, intermediate grade (G2), respectively. Histologically, typical carcinoids have less than 2 mitoses per square millimeter and lack necrosis, whereas atypical carcinoids have 2 to